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(54) CAPSULES AND OTHER SELF-SUPPORTING MEDICINAL PACKAGING MEANS

(71) We, SOCIETE D'ETUDES, DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ET MEDICALES (E.R.A.S.M.E.) a French Company of 67, Avenue De Wagram, 75-Paris 17E, France and RENE CLAUDE, a citizen of France, of 13, Rue Des Hauts-Closeaux, 92-Sevres (Hauts De Seine), France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to capsules and like self-supporting medicinal dosage forms comprising a shell formed of thermoplastic and to processes for producing the same.

Gelatine capsules have been in use for many years as a medicinal dosage form. It has recently been suggested that gelatine be replaced by certain other polymeric substances such as hydroxyalkylcelluloses. In both these cases the production process consists of immersing a capsule-forming mould into a solution of the polymeric substance (gelatine or hydroxyalkylcellulose), withdrawing the mould from the solution so as to obtain, on the mould surface, a substantially uniform coating of the solution, and drying this coating to form a self-supporting film or skin which constitutes a capsule.

It is also known that coated tablets or powders may be produced by impregnating tablets or powders with a solution or dispersion of at least one polymeric substance, and then drying the impregnated tablets or powders to form a film of the polymeric substance(s) covering the tablets or powders.

As will have been appreciated the processes described in the two preceding paragraphs are "wet" processes. They incur substantial disadvantages which may be eliminated or reduced by the present invention.

It has been suggested to produce threads or packagings for medical use by plastic conversion of polyvinyl alcohol, but it was found that plastic conversion of polyvinyl alcohol by conventional processes for conversion of plastics materials produced a product which was of low solubility or insoluble, and which was brittle and not suitable for use in capsules.

The present invention renders possible the industrial production of self-supporting medicinal dosage forms such as capsules which may be administered together with medicines which they contain and which dissolve, disintegrate or become porous within the human body, thereby releasing the medicines.

The invention provides a process for producing capsules and like pharmaceutical dosage forms having a medicinally-inert shell comprising shaping by fusion in the absence of a solvent at least one thermoplastics selected from the following specified materials to form a medicinally-inert shell having sufficient thickness so that it is self supporting.

(a) Vinylpyrrolidone/vinyl acetate copolymers
(b) Polyacrylic acid;
(c) polymethacrylates;
(d) polyoxyethylene having a molecular weight between 600,000 and 4,000,000;
(e) hydroxypropyl cellulose; and
(f) polyvinyl alcohol having an ester index higher than 200.

These thermoplastics should be pharmaceutically acceptable. In some cases, they should dissolve or disintegrate in a selected region of the digestive tract. They should above all be workable and able to be formed to shape whilst in the plastic state by industrial processes which allow the production of capsules and packaging means in very great numbers.

The shaping may be performed by injection, moulding, heat-forming or depositing and fusing powder on an arbour.

It is envisaged that the capsules or other self-supporting dosage forms may be administered orally, rectally or vaginally and the shell will dissolve, disintegrate or become porous under the action of the physiological

environment thereby releasing medicament contained in the shell.

A thermoplastics usable according to the invention should be non-toxic, and should (in some cases) dissolve or disintegrate in a selected region of the digestive tract. They must also complementarily be able to withstand conversions and forming to shape in the molten or fused state so that the self-supporting capsules or other packaging means can be produced on an industrial scale. This is the reason why, among the thermoplastics corresponding to the above criteria, the applicants have chosen a particular group of thermoplastics according to the invention, these thermoplastics may be employed singly, or mixed with each other, or with additives, such as plasticisers, antioxidants and release agents.

According to the invention, it is thus possible to employ vinylpyrrolidone/acetate copolymers. The preferred copolymer has a vinylpyrrolidone/vinyl acetate ratio of 60:40, a density of approximately 1.27 and a melting point of approximately 165°C. These copolymers are water soluble within a very wide pH range; they are preferably employed with plasticisers, among which may be mentioned dioctyl phthalate, glycerin and sorbitol and with release agents such as stearamide, oleamide and calcium stearate, and with conventional anti-oxidants. They may be used alone or mixed with other plastics materials applicable according to the invention, in particular with polyvinyl alcohols having a higher ester index than 200, and polyacrylic acid, or even with other compatable plastics materials such as cellulose polyacetate. The copolymers of vinylpyrrolidone and of vinylacetate may be applied according to the invention by means of the different processes specified, in which the fusion of the product plays a part; the tests performed have shown however that these coplymers were more particularly appropriate for the injection-moulding process.

It is equally possible to employ polyacrylic acid alone or mixed with additive such as plasticisers, anti-oxidants and/or release agents. Polyacrylic acid may be mixed with other thermoplastic materials according to the invention and more specifically with the copolymers of vinylpyrrolidone and vinyl acetate. This polyacrylic acid usable for the production of self-supporting capsules or other packaging means according to the invention and whose melting point is of approximately 120 to 135°C, has the property of being soluble in a weakly alkaline environment and insoluble in an acid environment; it is thus possible by application of this polymer, to produce gastro-resistive and entero-soluble capsules or packaging means. Packaging means possessing properties of this nature are unknown at present.

Polymethyacrylates are equally applicable according to the invention. The preferred methacrylate polymers are: polybutylmethacrylate and polydimethylaminoethyl methacrylate which is soluble in an acid environment and is consequently suitable for the production of dosage forms which are soluble or dispersible in the stomach, and the copolymers of methyl methacrylate and of methacrylic acid which, depending on their methacrylic acid content, become soluble in a basic environment and consequently become viable for the production of capsules or packaging means which do not dissolve or disintegrate except in an intestinal environment. As with the other polymeric substances applicable according to the invention these polymethacrylates and copolymers may be employed mixed with different additives and with different other polymeric substances such as polyoxyethylenes or polyvinyl acetate.

It is equally possible to employ the polyoxyethylenes having a molecular weight between 600,000 and 4,000,000. Such polymers proved to be particularly appropriate for application by the heat-moulding process even without employing plasticisers. To increase the rigidity of the material, fillers having a reinforcing action such as silica, kaolin or chalk may be incorporated into the polyoxyethylenes. The polyoxyethylenes may be mixed with other plastic materials such as polyacrylic or polycarboxyvinyl substances, with which it forms complex polymeric substances.

A hydroxypropylcellulose having a mean molecular weight Mw = 275,000 is equally employed. This material simultaneously has the properties of solubility thermoplasticity and surface-activity. Owing to this fact, it is wholly suitable for injection moulding owing to its qualities of fluidity when hot, and of anti-adhesion capacity. It has been observed that the grades having a high molecular weight (Mw = 900,000) are brittle, and those having a low molecular weight (Mw = 75,000) are soft. Thanks to the self-lubricating nature of the substance, plasticising is unnecessary. The incorporation of an anti-oxidant, for example Irganox 1076 (0.2%) prevents discolouration of the product at high temperature.

It has been discovered that hydroxypropylcellulose is equally appropriate for extrusion of plates and for heat-moulding. It is compatible, in particular, with polyoxyethylene, the other cellulose derivatives, and gelatine.

Finally, according to the invention, it is equally possible to employ a polyvinyl alcohol having a high ester index, of the order of 200 to 300, or a molecular degree of hydrolysis of 70 to 80%. The polymer in the form of powder of a fineness between 100 and 200 microns, is deposited by means of a spraygun of a fluidised bed on an arbour heated to 320°C. The grade of powder most suitable for this application has a density of 1.27 to 1.30 and a melting point of approximately 130°C. To prevent thermal degradation of the

polyvinyl alcohol employed in this process, it is appropriate to protect the same by incorporation of up to 0.4% of " Irganox 1076 ". It has been observed that the release agents which are surface active as a rule, should be excluded from the composition of the mixtures, owing to the fact that they raise the risk of delaying the agglomeration of the plastic powders and their fusion. To improve the fluidity of the polymeric substances in the molten state, a plasticiser (5%) such as glycerine or propyleneglycol, may be added to the polymer.

If it is intended, for production of self-supporting capsules and dosage forms, to employ polyvinyl alcohol, it is necessary to make an appropriate choice of the initial polymeric substance and equally of the process for conversion of this initial material. If these choices are inappropriate and do not correspond to the invention, packaging elements which are insoluble or non-disintegrable are frequently obtained, since the initial material has undergone a definite number of chemical conversion such as, for example reticulations.

The invention is illustrated by the following Examples.

Example 1

In a mixer of the " belt " type, heated to 60°C, a mixture of the following ingredients was prepared:

Polyvinylpyrrolidone/vinyl acetate copolymer (density 1.27, melting point 165°C)	100 g
Stearamide (release agent).	6 parts by weight
Irganox 1076 (anti-oxidant)	0.4 „ „ „
Dioctyl phthalate (plasticiser)	30 „ „ „

Capsules were produced by injection moulding of this mixture with a piston press heated to 170°C, using a pressure of 1000 kgs/cm². The capsules were rigid; smooth and shiny, and had a length of 16.7 mms, a diameter of 6.6 mms and a wall-thickness of 0.1 mm.

Sheets having a thickness of 1 mm were produced on an extrusion press equipped with a flat (orifice) die-plate, which were employed to produce capsules by heat-moulding.

Example 2

A homogenising operation was performed in a bladed mixer on a mixture having the following composition:

Polyacrylic resin (density 1.2 — melting point 122°C—135°C)	100 g
Stearamide (release agent)	4 parts by weight
Irganox 1076 (anti-oxidant)	0.4 „ „ „

Capsules were made by injection moulding from this homogenised mixture on a piston press, at 180°C and at a pressure of 1200 kgs/cm². The capsules were accurately dimensioned.

Sheets of the homogenised mixture having a thickness of 1 mm, a width of 180 mms, were extruded by means of the extrusion press used in Example 1. The sheets were smooth, uniform and incurred little transversal contraction. The heating temperatures were: 150°C in the barrel, 170° at the head, 180°C at the die-plate. Heat-moulding was applied on these sheets to produce capsules. Tubes having a diameter of 6.65 mms and a wall-thickness of 1.1 mm were extruded on the same extrusion press equipped with a tube-drawing die on this occasion. These were cut into sections of 16.70 mms and moulded at one extremity by means of a heating electrode having the shape of a spherical cap, to produce capsules.

Example 3

A mixer of the " belt " type, heated to 50°, was employed to produce a mixture of two polymers in equal proportions (50/50): polyacrylic resin and polyvinylpyrrolidone/vinyl acetate copolymer.

Polyacrylic resin	50 g
Polyvinylpyrrolidone/vinyl acetate copolymer	50 g
Stearamide (release agent)	3 g
IRGANOX 1076 (anti-oxidant)	0.2 g
Dioctyl phthalate (plasticiser)	20 g

A moulding operation was performed after homogenisation under heat, at a temperature of 170°C. Plates were obtained, which were smooth, uniform, homogeneous, rigid but not brittle.

An extrusion press equipped with a flat nozzle was employed to extrude sheets from this mixture, which had a thickness of 1 mm, were homogeneous, non-adhesive, and of smooth appearance.

The conditions of extrusion were the following:

Heating temperatures — barrel: 165°C — Head: 180,C — Nozzle: 170°C.

Self-supporting capsules and dosage forms were produced by heat-moulding from the sheets obtained by compression or extrusion.

Example 4

A paddle mixer was used to prepare a mixture consisting of:

Polymethacrylate of butyl and of dimethylaminoethyl (melting point 122°C)	100 g
Stearamide (release agent)	4 parts by weight
Irganox 1076 (anti-oxidant)	0.4 „ „ „

Injection mouldings were produced from this mixture on a piston press at 160°C and at a pressure of 1200 kgs/cm². Capsules having the aforesaid dimensions were obtained. An extrusion press equipped with a flat nozzle as specified above, was employed with the same mixture to extrude sheets having a thickness of 0.5 mm and of 1 mm, and a width of

160 mms. These sheets were shiny and transparent. Capsules were produced by heat-moulding from these sheets.

Tubes having the aforesaid dimensions were extruded on the same extrusion press, equipped with a tube-drawing die on this occasion. After cooling and calibrating in a calibrating tool at the temperature of 50°C, the tubes were cut into sections of 16.70 mms and moulded at one end by means of a heating electrode having the shape of a spherical cap, to obtain self-supporting capsules.

The conditions of tube extrusion were:
Heating temperature of the extrusion press:
Barrel: 130°C — Head 150°C — Die: 140°C.
Speed of extrusion: 5 m/minute.

Plates having a thickness of 1 mm, which were shiny and transparent, were equally moulded from the mixture by compression at a temperature of 160°C and under a pressure of 300 kgs/cm². Self-supporting capsules were produced by heat-moulding from the plates.

Example 5

A paddle mixer was used to prepare a mixture consisting of:

Polyoxyethylene (melting point 70° — molecular weight 4,000,000)	100 g
Stearamide (anti-adhesive agent)	5 parts by weight
Irganox 1076 (anti-oxidant)	0.15 „ „ „
Titanium oxide (filler)	2 „ „ „

Capsules having the aforesaid dimensions were injection-moulded from this mixture at a temperature of 200° under a pressure of 1300 kgs/cm². The capsules retained their initial shape after storage. As an alternative, an extrusion press equipped with a flat nozzle whose characteristics have been mentioned above, was equally employed to extrude sheets of the mixture, having a thickness of 1 mm and of 1.5 mm, from which were produced capsules by heat-moulding by means of a plunger of a length of 16.70 mms.

Example 6

A paddle mixer was used to prepare a mixture consisting of:

Hydroxypropylcellulose (molecular weight 275,000; softening point: 130°C)	100 g
Stearamide (release agent)	4 g
Butyl hydroxyanisol (anti-oxidant)	0.02 g

Capsules were injection-moulded at a pressure of 880 kgs/cm² and at a temperature of 180°C. The capsules obtained were rigid, transparent, shiny and incurred little contraction and no deformation at all and were not affected by humidity after being stored for 48 hrs. in an ambient atmosphere. The capsules were not easily breakable.

Example 7

A " band " mixer was employed to prepare:

Polyvinyl alcohol (ester index 270, density 1.2, melting point 130°C)	100 g
Stearamide (release agent)	4 parts by weight
Irganox 1076 (2) (anti-oxidant)	0.2 „ „ „
Dibutyl phthalate (plasticiser)	10 „ „ „
Titanium oxide (filler)	4 „ „ „

Capsules were injection moulded from this mixture on a piston press at 190°C, and under a pressure of 1300 kgs/cm². The capsules had a length of 16.70 mms, a diameter of 6.65 mms, and a wall-thickness of 1/10 mm. As an alternative, this same mixture was extruded in sheet form by means of an extrusion press having a screw of a diameter of 25 mms and a length equal to 25 diameters, equipped with a flat nozzle having a die-slot of 200 mms length and a width of 2 mms. The heating temperatures of the extrusion press were: 140°C in the barrel, 175°C at the head, and 170°C at the nozzle. Sheets were obtained, having a thickness of 1mm, and a width of 150 mm. The sheets were then formed into capsules. Plates having a thickness of 1 mm were moulded by compression from the same, nonplasticised, mixture at the temperature of 170°C and under a pressure of 270 kgs/cm². The plates were rigid, transparent, slightly brittle but not adhesive and possessed the following mechanical characteristics:
Breaking strain: 350 kgs/cm² — elongation: 180%.

The plates thus obtained were converted by stamping to a depth of 16.70 mms and capsule shells formed. The same mixture was deposited by fluidisation on a punch previously heated to 280°C. The powder became agglomerated on the punch to form a self-supporting shell.

Example 8

A film of polyvinyl alcohol obtained from a substance having a mean ester index exceeding 200 was heated to approximately 140°C, was heat-moulded to produce dosage forms having a diameter of approximately 10 mms and a depth of approximately 5 mms. The forms disintegrated easily in water and were suitable for packaging medicines which should be released from their packages in the stomach.

Different capsules or dosage forms were also made with the following mixtures:

polyvinyl alcohol	90 %
polyvinyl acetate	10 %
polyvinyl alcohol	85 %
polyvinyl acetate	10 %
glycerine	5 %
polyvinyl alcohol	85 %
butyl methacrylate	7.5 %
polydimethylaminoethylmethacrylate	7.5 %

The result obtained with the different capsules or dosage forms thus produced are similar to those obtained from the film of polyvinyl alcohol described above.

Example 9

A powder consisting of vinylpyrrolidone/vinyl acetate copolymer containing 40% of vinyl acetate was fed into a mould-heated to approximately 100°C (that is to say to the softening point of the copolymer). A cold punch was inserted into the mould and a small cylindrical capsule was formed by flowage and and agglomeration of the powder. The capsule had a diameter of 6.5 mms and a depth of 17 mms and one end of it was open.

The capsule was water-soluble.

Mixtures of the same copolymer with plasticisers or colourants or fillers of various kinds, such as other plastics materials such as carboxyvinyl polymers, copolymers of ethylene and of maleic anhydride, may be employed according to the same technique.

Example 10

The solubilities of capsules produced in the foregoing Examples were measured in different environments. The different environments were: water, artificial gastric juices, and artificial intestinal juices, at a temperature of 37°C ± 2°C. The capsules were exposed to continuous vertical agitation. The periods of dissolution of the capsules were measured.

The formulae applied in the production of the secretions were:

artificial gastric juices	
NaCl	2 g
pepsin	3.2 g
HCl	7 ml
distilled water to	1000 ml

artificial intestinal juices	
monopotassium phosphate	6.8 g
pancreatine	10 g
0.2 N NaOH	190 ml
distilled H_2O	600 ml

Nature of the Capsules	Periods of Dissolution: water	artificial gastric secretions (pH 1)	artificial intestinal secretions (pH 7.5)	Remarks
1) polyvinyl alcohol	12 minutes	15 minutes	20 minutes	complete dissolution
2) polyoxyethylene	15 „	12 „	10 „	„
3) polyacrylic	insoluble	insoluble	85 „	partial dissolution
4) polymethacrylate of butyl and dimethyl-aminoethyl	2 hours	5 minutes	2 hours	complete dissolution
5) polyvinylpyrrolidone/vonyl acetate	12 minutes	15 „	10 minutes	complete dissolution
6) PVP-VA/polyacrylic	2 hours	low solubility	45 mins.	partial dissolution
7) hydroxypropyl-cellulose	10 mins.	20 mins.	15 mins.	complete dissolution

The solubility test was performed on the apparatus specified in USP XVI standard for tests covering disintegration of tablets.

WHAT WE CLAIM IS:—

1. A process for producing capsules and like pharmaceutical dosage forms having a medicinally-inert shell comprising shaping by fusion in the absence of a solvent at least one thermoplastic selected from the following specified materials to form a medicinally-inert shell having sufficient thickness so that it is self supporting:

(a) vinylpyrrolidone/vinyl acetate copolymers
(b) polyacrylic acid;
(c) polymethacrylates;

(d) polyoxyethylene having a molecular weight between 600,000 and 4,000,000;
(e) hydroxypropyl cellulose; and
(f) polyvinyl alcohol having an ester index higher than 200.

2. A process as claimed in claim 1, wherein the thermoplastic contains at least one additive selected from plasticizers, release agents, antioxidants and fillers.

3. A process as claimed in claim 1 or 2, wherein the thermoplastic is a vinylppyrrolidine/vinyl acetate copolymer and the shaping is performed by injection-moulding.

4. A process as claimed in claim 1 or 2, wherein the thermoplastic is polyacrylic acid and the shaping is performed by heat-moulding.

5. A process as claimed in claim 1 or 2, wherein the thermoplastic is a homopolymer or copolymer of methacrylate and the shaping is performed by hot-forming of an extruded thin-walled tube.

6. A process as claimed in claim 1 or 2, wherein the thermoplastic is polyoxyethylene and the shaping is performed by heat-moulding.

7. A process as claimed in claim 1 or 2, wherein the thermoplastic is hydroxypropyl cellulose and the shaping is performed by injection-moulding.

8. A process for producing self-supporting medicinal packaging means in encapsulated form substantially as described herein with reference to any one of Examples 1 to 9.

9. Self-supporting medicinal packaging means in encapsulated form produced by a process as claimed in any one of claims 1 to 8.

MARKS & CLERK

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